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(54) Title: FAST DISSOLVING DOSAGE FORMS CONTAINING MAGNESIUM ALUMINUM SILICATE AND MULTIPLE ACTIVE INGREDIENTS

(57) Abstract

An adsorbate composition comprising magnesium aluminum silicate and two or more pharmaceutically acceptable actives in a fast dissolving dosage form.

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FAST DISSOLVING DOSAGE FORMS CONTAINING MAGNESIUM ALUMINUM SILICATE AND MULTIPLE ACTIVE INGREDIENTS

TECHNICAL FIELD

The present invention relates to a good tasting, fast dissolving adsorbate composition consisting of magnesium aluminum silicate with two or more pharmaceutically acceptable active ingredients.

BACKGROUND OF THE INVENTION

Adsorbates have been used for many years, masking the untoward taste of many compounds. The use of magnesium aluminum silicate in this capacity is disclosed in, for example, U.S. Patent 4,711,774, December 8, 1987; 4,716,033, December 29, 1987; 4,758,424, July 19,1988; 4,758,425, July 19,1988; 4,761,274, August 2,1988 to Denick, Jr. et al., U.S. Patent 4,753,800, June 28, 1988 to Mozda and U.S. Patent 3,140,978, July 14, 1964 to Zentner.

While the prior art discloses magnesium aluminum silicate as useful in masking the taste of pharmacologically active compounds, there is still a need for fast dissolving, taste-masking formulations of this kind incorporating multiple pharmacologic actives. The prior art disclosures of immediate release dosage forms containing magnesium aluminum silicate as the taste masking agent generally focus on masking the taste of a single pharmaceutically active ingredient. This may be attributed to the assumption that any increase in the amount of the bitter tasting component(s) used (e.g. higher doses of the initial compound or the admixing of an additional compound(s)) would require a corresponding increase in the amount of magnesium aluminum silicate used. The causal link between this assumption and the focus of the prior art becomes evident as one appreciates the problems that arise with increasing amounts of magnesium aluminum silicate. These problems include decreased disintegration time, decreased release of the pharmaceutically active ingredient and decreased palatability (i.e. experiencing an undesirable clay taste). The present inventors, however, have discovered that despite the presence of multiple, pharmaceutically active compounds, fast dissolving dosage forms which incorporate a single taste masking agent, magnesium aluminum silicate, still retain their taste masking ability even at levels low enough to avoid the above-mentioned problems. It is therefore an object of the present invention to provide a good-tasting adsorbate composition that contains two or more pharmacologic actives. It is a further object of the present invention to provide a good-tasting, fast dissolving composition incorporating said pharmaceutical actives. Still a further object is to provide a

method of making a good tasting, quick dissolving medicament containing multiple pharmaceutical actives.

These objectives and additional objectives will become readily apparent from the detailed description which follows.

SUMMARY OF THE INVENTION

The present invention relates to a pharmaceutical composition comprising:

(a) a clay component consisting of magnesium aluminum silicate;

(b) a safe and effective amount of two or more pharmaceutically acceptable active ingredients selected from the group consisting of: an antitussive; an antinauseant; a nutritional supplement; a laxative; an appetite suppressant; an analgesic; an antiasthmatic; an antihistamine; a decongestant; an expectorant; an antacid; an antidiarrheal, a H_2-Receptor antagonist and mixtures thereof; and

(c) a pharmaceutically acceptable carrier

wherein said pharmaceutically acceptable carrier can be rapidly disintegrated in aqueous solution.

The present invention further relates to methods of treating symptoms such as those associated with the common cold, respiratory disorders, cough, cold, cold-like and/or flu symptoms associated with the common cold, gastrointestinal disorders and allergies; comprising the administration of a safe and effective amount of the compositions of the present invention.

All percentages and ratios herein are by weight unless otherwise specified. Additionally, all measurements are made at 25°C unless otherwise specified.

By "safe and effective amount," as used herein, is an amount that is effective to mitigate and/or treat the symptoms for which the active ingredient is indicated in a human without undue adverse side effects commensurate with a reasonable risk/benefit ratio.

DETAILED DESCRIPTION OF THE INVENTION

The compositions of the present invention contain essential components as well as various nonessential components as indicated below.

ESSENTIAL COMPONENTS

Magnesium Aluminum Silicate

The first essential component of the present invention is a safe and effective amount of magnesium aluminum silicate of the formula $Al_2MgO_8Si_2$. Magnesium aluminum silicate occurs naturally in such smectite minerals as colerainite, saponite, sapphirine, sheridanite zebedassite and has been used extensively in a variety of cos-

metic and pharmaceutical formulations. The refined magnesium aluminum silicates used in the present example, Veegum® HS, is available from and manufactured by R.T. Vanderbilt Company, Inc., Norwalk, CT. A Typical chemical analysis of Veegum® HS, is as follows:

Silicon dioxide	63.0
Magnesium oxide	10.5
Aluminum oxide	10.5
Ferric oxide	0.9
Calcium oxide	2.3
Sodium oxide	2.4
Potassium oxide	1.2
Ignition loss	7.5

having a combined density of 2.6mg/m^2.

The compositions of this invention typically comprise from about 0.01% to about 50%, preferably from about 0.1% to about 25%, more preferably from about 1.0% to about 10% and most preferably from about 1.0% to about 5%, by weight of a magnesium aluminum silicate.

Magnesium aluminum silicates are described more fully in, for example, U.S. Patent 4,761,274, August 2, 1988, to Denick, Jr. et al.; U.S. Patent 4,753,800, June 28, 1988, to Mozda, and U.S. Patent 3,140,978, July 14, 1964 to Zentner; all of which are herein incorporated by reference.

Pharmaceutically acceptable actives

The two or more pharmaceutically acceptable actives useful in the present invention may be selected from among the various groups of chemical compounds or materials suitable for oral administration and having a pharmacological action. These pharmaceutically acceptable active compounds or materials should be compatible with the other essential ingredients and compatible in combination with other included active materials or compounds. The pharmaceutically acceptable active compounds or materials are present at a level from about 0.01% to about 75%, preferably from about 0.1% to about 50%, more preferably from about 1.0% to about 25% and most preferably from about 1.0% to about 10%. Useful pharmaceutically acceptable active materials or compounds may include, but are not limited to: bronchodilators, anorexiants, antihistamines, nutritional supplements (such as vitamins, minerals, fatty acids, amino acids, and the like), laxatives, analgesics, antacids, H_2-receptor antagonists, antidiarrheals, decongestants, antitussives, antinauseants, antimicrobials, antifungals, antivirals, expectorants, anti-inflammatory agents, antipyretics, their pharmaceutically acceptable salts and mixtures thereof.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include sodium, potassium, lithium, ammonia, calcium, magnesium, ferrous, zinc, manganous, aluminum, ferric, manganic salts and the like. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, tertiary and quaternary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as triethylamine, tripropylamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, lysine, arginine, histidine, caffeine, procaine, N-ethylpiperidine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglycamine, theobromine, purines, piperazine, piperidine, polyamine resins and the like.

Examples of decongestants useful in the compositions of the present invention include pseudoephedrine, phenylpropanolamine, phenylephrine and ephedrine, their pharmaceutically acceptable salts, and mixtures thereof.

Examples of antitussives useful in the compositions of the present invention include dextromethorphan, chlopedianol, carbetapentane, caramiphen, noscapine, diphenhydramine, codeine, hydrocodone, hydromorphone, their pharmaceutically acceptable salts, and mixtures thereof.

Examples of expectorants (also known as mucolytic agents) useful in the present invention include; glyceryl guaiacolate, terpin hydrate, ammonium chloride, N-acetylcysteine, and ambroxol, their pharmaceutically acceptable salts, and mixtures thereof.

Examples of analgesics useful in the present invention include; morphine, codeine, meperidine, pentazocine, propoxyphene, acetaminophen, allopurinol, acetylsalicylic acid, choline salicylate, ketoprofen, magnesium silicate, fenoprofen, ibuprofen, indomethacin, naproxen, and many others and their pharmaceutically acceptable salts and mixtures thereof.

Examples of antihistamines useful in the present invention include; brompheniramine, chlorpheniramine, clemastine, dexchlorpheniramine, diphenhydramine, doxylamine, promethazine, terfenadine, triprolidine and many others and their pharmaceutically acceptable salts and mixtures thereof.

Analgesics, decongestants, antihistamines, expectorants and antitussives, as well as their acceptable dosage ranges are described in U.S. Patent 4,783,465 to Sunshine et al., issued November 8, 1988, and U.S. Patent 4,619,934 to Sunshine et al., issued October 28, 1986, which are incorporated by reference herein.

Examples of gastrointestinal agents suitable for use in the present invention include anticholinergics, including atropine, clidinium and dicyclomine; antacids, in-

cluding aluminum hydroxide, bismuth subsalicylate, simethicone, calcium carbonate and magaldrate; H_2-receptor antagonists including: cimetidine, famotidine, nizatidine and ranitidine; laxatives, including: phenolphthalein and casanthrol; and antidiarrheals including: diphenoxylate and loperamide.

Further examples of suitable analgesics, decongestants, antitussives, expectorants and antihistamines as well as bronchodilators, anorexiants, laxatives, antiemetics, antimicrobials, antibacterials, antifungals, anti-inflammatory agents, antivirals, antipyretics, nutritional supplements, anticholinergics, antacids, H_2-receptor antagonists, antidiarrheals and other miscellaneous gastrointestinal compounds and their acceptable dosage ranges are described in Remington's Pharmaceutical Sciences, pp. 734-789, 791-799, 861-868, 907-945, 875-888, 1002-1034, 1098-1121, 1124-1131, 1173-1224, 1232-1241, (Alfonso R.Gennaro, editor) (18th ed. 1990), herein incorporated by reference.

NONESSENTIAL COMPONENTS

Persons skilled in the art will quickly realize many other ingredients will be suitable for inclusion into the present invention. Nonessential components include, but are not limited to: coloring agents; flavoring agents, including: vanilla, cherry, grape, orange, peppermint, spearmint, anise, blueberry raspberry, banana, chocolate, caramel, strawberry, lemon, menthol and Prosweet™ MM50 (a combination of natural and artificial flavors and propylene glycol, available from Virginia Dare Extract Co., Inc., Brooklyn, NY); sweeteners, including saccharin, dextrose, levulose, sucrose, cyclamate, mannitol and aspartate, along with many others; suspending agents, including xanthum gum, acacia gum, carboxymethylcellulose, starch and methylcellulose; preservatives; releasing agents, including polysorbate 80, sodium lauryl sulfate, vegetable oils and magnesium stearate; and water.

Another preferred nonessential component of the present invention is a cooling agent or a combination of cooling agents. Suitable cooling agents are those described in U.S. Patent 4,136,163, January 23, 1979, to Watson et al., U.S. Patent 4,230,668, October 28, 1980, to Rowsell et al. and U.S. Patent 4,032,661, to Rowsell et al., all of which are herein incorporated by reference. A particularly preferred cooling agent is N-ethyl-p-menthane-3-carboxamide (WS-3 supplied by Sterling Organics), taught by the above incorporated U.S. Patent 4,136,163. Another particularly preferred cooling agent is 3-1-menthoxypropane 1,2-diol (TK-10 supplied by Takasago Perfumery Co., Ltd., Tokyo, Japan). This material is described in detail in U.S. Patent 4,459,425, July 10, 1984 to Amano et al. and incorporated herein by reference.

METHOD OF MANUFACTURE

Good tasting pharmaceutical adsorbate compositions of the present invention are prepared using art-recognized principles and methodologies in mixing the ingredients together and in choosing the type of mixing equipment to be used. However, because of the potential for adverse interactions between the magnesium aluminum silicate and various multiply charged cationic drugs (e.g. chlorpheniramine) - resulting in poor drug dissolution, it is important that certain measures be followed to insure effective drug dissolution. Such a situation is described in McGinty, J.W. and Lach, J.L., In Vitro Adsorption of Various Pharmaceuticals to Montmorillonite, Jour. of Pharm. Sci., 65, 896-902 (1976) and is herein incorporated by reference. By "multiply charged cationic drugs" as used herein, means compounds containing more than one positively charged substituent. The crucial steps involve maintaining the pH in a range equal to or above that of the pKa of the multiply charged cationic drug(s) and, additionally, reserving the addition of said multiply charged cationic drug(s) until after the addition of at least one other cationic compound.

After the ingredients of the present invention are combined, the mixture may then be compounded with effervescent or other water-dispersible substances and dried into dosage forms that rapidly disintegrate upon coming into contact with an aqueous liquid. Suitable effervescent technology is described in chapter 6 of Pharmaceutical Dosage Forms: Tablets, Vol. I, 2nd ed., A Lieberman ed., 1989, Marcel Dekker, Inc. herein incorporated by reference. The above mentioned compounding and drying process may be accomplished by using any of a multitude of solid dosage forming techniques and equipment. Methods of solid dosage formulation are well known in the art and any appropriate method may be utilized. Further information regarding solid dosage formulation can be found in Remington's Pharmaceutical Sciences, pp. 1633-1664, (Alfonso R. Gennaro, editor) (18th ed. 1990).

Alternatively, the resultant fast dissolving dosage form may be achieved by freeze drying. Freeze-drying or lyophilization facilitates disintegration of the composition by forming the dried composition into an open matrix network. In most cases, this results in rapid permeation by the aqueous media, promoting timely delivery of the product's active ingredients. Suitable methods of freeze drying are well known in the art and commonly employed. Any suitable conventional method of freeze-drying or vacuum-drying may be utilized. A preferable method of freezing and drying is to fast freeze the composition and then dry the composition to a final moisture content of about 2% to about 5%. Suitable methods of freeze-drying and production are taught by U.S. Patent 4,642,903, February 17, 1987, to Davies, U.S. Patent 4,946,684, August 7, 1990, to Blank et al., U.S. Patents 4,305,502 and

4,371,516, issued December 15, 1981 and February 1, 1983 respectively, to Gregory et al., and U.S. Patent 5,188,825, February 23,1993, to Iles et al.; which are all incorporated herein by reference

One other form of fast dissolving technology that may be applicable to the present invention is that developed by Janssen Pharmaceutica Inc. and is identified by the trade name Quicksolv™. This technology is fully described in U.S. Patent 5,215,756, herein incorporated by reference.

EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations are possible without departing from the spirit and scope of the invention.

EXAMPLE I

Ingredients	W/V%
chlorpheniramine maleate	0.13300
phenylpropanolamine HCl	0.83300
magnesium aluminum silicate[1]	0.50000
xanthum gum	0.20000
potassium sorbate	0.07500
polysorbate 80	0.10000
Prosweet™ MM24[2]	0.50000
sodium saccharin	0.05000
aspartame	0.30000
monoammonium glycyrrhizate[3]	0.03000
sucrose	5.00000
mannitol	10.00000
3-1-menthoxypropane 1,2-diol[4]	0.07000
N-ethyl-p-menthane-3-carboxamide[5]	0.02000
menthol, natural	0.26600
peppermint flavor	0.18000
purified water	q.s. to 100

[1]Available as Veegum® HS from R.T. Vanderbilt, Norwalk, CT.

[2]Available from Virginia Dare Extract Co., Inc., Brooklyn, NY.

[3]Available as Magnasweet 185 supplied by McAndrews & Forbes, Camden, NJ.

[4]Available as TK-10 supplied by Takasago Perfumery Co.

[5]Available as WS-3 supplied by Sterling Organics.

In an appropriately sized container, with Lightnin™ mixer (model #TS2010 (or a high shear homogenizer set at 30 to 50 RPM)) mixing at approximately 250 to 1000 RPM, add the following agents allowing each to dissolve before adding the next: water, phenylpropanolamine HCl, Veegum® HS. Heat, using a hot plate, keeping solution at 77°C, and mix vigorously (250 to 1000 RPM) for 30 minutes. Turn heat off and allow mixture to cool to room temperature (25°C) while mixing for a minimum of an additional 15 minutes. Add monoammonium glycyrrhizate, Prosweet™ MM24, potassium sorbate, aspartame, sodium saccharin, WS-3 and peppermint.

Separately, dry blend mannitol, sucrose, and xanthum gum and add slowly to the original mixture. Separately dissolve chlorpheniramine maleate with a sufficient amount of water and add to the original mixture. Adjust the volume to 1.5000 liters and mix for 15 minutes. Separate from the above mixture, in an appropriate container, add polysorbate 80, TK-10, and menthol. Add this mixture to the original mixture while continuing mixing. As the mixing continues, place 1.5 ml of solution into molds and freeze-dry or vacuum-dry the composition. This process, in turn, provides a pharmaceutical adsorbate composition having improved taste. Administration of two tablets to an adult human is the normal and customary dosage for use in treating the symptoms of a respiratory illness or allergy.

EXAMPLE II

Ingredients	W/V%
chlorpheniramine maleate	0.13300
phenylpropanolamine HCl	0.83300
magnesium aluminum silicate	0.50000
xanthum gum	0.20000
potassium sorbate	0.07500
polysorbate 80	0.10000
Prosweet™ MM24	0.50000
sodium saccharin	0.05000
aspartame	0.30000
monoammonium glycyrrhizate	0.03000
sucrose	5.00000
mannitol	10.00000
3-1-menthoxypropane 1,2-diol	0.07000
N-ethyl-p-menthane-3-carboxamide	0.02000
menthol, natural	0.26600
lemon flavor	0.40000

color, FD&C Yellow #6	0.00240
purified water	q.s. to 100

EXAMPLE III

Ingredients	W/V%
chlorpheniramine maleate	0.13300
phenylpropanolamine HCl	0.83300
magnesium aluminum silicate	0.50000
xanthum gum	0.20000
potassium sorbate	0.07500
polysorbate 80	0.10000
Prosweet™ MM24	0.50000
sodium saccharin	0.05000
aspartame	0.30000
monoammonium glycyrrhizate	0.03000
sucrose	5.00000
mannitol	10.00000
3-1-menthoxypropane 1,2-diol	0.07000
N-ethyl-p-menthane-3-carboxamide	0.02000
menthol, natural	0.26600
raspberry flavor	0.30000
color, FD&C Yellow #6	0.00236
color, FD&C Red #33	0.00326
purified water	q.s. to 100

EXAMPLE IV

Ingredients	W/V%
diphenhydramine HCl	0.83300
phenylpropanolamine HCl	0.83300
magnesium aluminum silicate	0.50000
xanthum gum	0.20000
potassium sorbate	0.07500
polysorbate 80	0.10000
Prosweet™ MM24	0.50000
sodium saccharin	0.15000
aspartame	0.30000
monoammonium glycyrrhizate	0.03000
sucrose	5.00000
mannitol	10.00000

3-1-menthoxypropane 1,2-diol	0.07000
N-ethyl-p-menthane-3-carboxamide	0.02000
menthol, natural	0.26600
lemon flavor	0.20000
menthol monophosphate	0.30000
purified water	q.s. to 100

EXAMPLE V

Ingredients	W/V%
triprolidine HCl	0.16700
phenylpropanolamine HCl	0.83300
magnesium aluminum silicate	0.50000
ascorbic acid	2.00000
xanthum gum	0.20000
potassium sorbate	0.07500
polysorbate 80	0.10000
Prosweet™ MM24	1.00000
sodium saccharin	0.15000
aspartame	1.00000
monoammonium glycyrrhizate	1.00000
sucrose	5.00000
mannitol	10.00000
3-1-menthoxypropane 1,2-diol	0.07000
N-ethyl-p-menthane-3-carboxamide	0.02000
menthol, natural	0.26600
lemon flavor	0.40000
purified water	q.s. to 100

EXAMPLE VI

Ingredients	W/V%
chlorpheniramine maleate	0.13300
phenylpropanolamine HCl	0.83300
magnesium aluminum silicate	2.00000
calcium carbonate[1]	0.80000
xanthum gum	0.20000
potassium sorbate	0.07500
polysorbate 80	0.10000
Prosweet™ MM24	0.50000
sodium saccharin	0.15000

aspartame	0.30000
monoammonium glycyrrhizate	0.03000
sucrose	5.00000
mannitol	10.00000
3-1-menthoxypropane 1,2-diol	0.07000
N-ethyl-p-menthane-3-carboxamide	0.02000
menthol, natural	0.26600
peppermint flavor	0.18000
purified water	q.s. to 100

[1]Granulated calcium carbonate containing 93.3% calcium carbonate, 6.3% glucose and 0.4% gelatin; supplied by Whittaker, Clark & Daniels, Philadelphia, PA.

Examples II-VI are further examples of combinations used in treating the symptoms of a respiratory illness or allergy in a human and are manufactured in a manner substantially similar to Example I. Administration of two tablets is the normal and customary dosage.

EXAMPLE VII

Ingredients	W/V%
magnesium aluminum silicate	8.48900
loperamide	2.44000
polysorbate 80	0.04000
sodium saccharin	0.05200
aspartame	0.05200
sucrose	14.00000
mannitol	12.25500
Novagel RCN-15[1]	1.60000
lemon Flavor	0.47200
vanilla Creme	0.15000
citric acid	0.45000
purified water	q.s. to 100

EXAMPLE VIII

Ingredients	W/V%
magnesium aluminum silicate	4.00000
bismuth subsalicylate	21.69930
polysorbate 80	0.03500
sodium saccharin	0.04550
aspartame	1.00000
sucrose	2.00000

mannitol	4.15000
Novagel RCN-15[1]	1.40000
strawberry flavor	0.54600
vanilla creme	0.54990
citric acid	0.06690
Klucel EF NF[2]	0.25200
Antifoam AF[3]	0.21000
purified water	q.s. to 100

EXAMPLE IX

Ingredients	W/V%
magnesium aluminum silicate	4.00000
simethicone	3.50000
polysorbate 80	0.03500
sodium saccharin	0.04550
aspartame	0.04550
sorbitol	0.70000
sucrose	8.25000
mannitol	16.29800
Novagel RCN-15[1]	1.40000
cherry flavor	0.19460
vanilla creme	0.24780
citric acid	0.28320
Antifoam AF[3]	0.21000
purified water	q.s. to 100

[1]Supplied by FMC Corporation, Philadelphia, Pennsylvania

[2]Supplied by AQUALON, Hopewell, Virginia

[3]Supplied by Dow Corning, Midland, Michigan

Examples VII -IX are further examples of combinations used in treating the symptoms of gastrointestinal illnesses in humans and are manufactured in a manner substantially similar to Example I. Administration of two tablets is the normal and customary dosage.

What is Claimed is:

1. A pharmaceutical composition comprising:
   (a) a clay component consisting of magnesium aluminum silicate;
   (b) a safe and effective amount of at least two pharmaceutically acceptable active ingredients selected from the group consisting of: an antitussive; an antinauseant; a nutritional supplement; a laxative; an appetite suppressant; an analgesic; an antiasthmatic; an antihistamine; a decongestant; an expectorant; an antacid; an antidiarrheal, a H_2-Receptor antagonist and mixtures thereof, preferably phenylpropanolamine and chlorpheniramine; and
   (c) a pharmaceutically acceptable carrier wherein said pharmaceutically acceptable carrier can be rapidly disintegrated in aqueous solution.

2. A pharmaceutical composition according to Claim 1 wherein said carrier is a freeze-dried matrix, an effervescent system, or a liquid/liquid extract system.

3. A pharmaceutical composition according to any one of the preceding Claims wherein the composition additionally contains one or more sweetening agents, preferably selected from the group consisting of sodium saccharin, aspartame, monoammonium glycyrrhizate, sucrose, mannitol and mixtures thereof.

4. A pharmaceutical composition according to any one of the preceding Claims wherein the composition additionally contains one or more flavoring agents.

5. A pharmaceutical composition according to any one of the preceding Claims wherein the composition additionally contains one or more releasing agents.

6. A pharmaceutical composition according to any one of the preceding Claims wherein the composition additionally contains one or more cooling agents.

7 A pharmaceutical composition according to any one of the preceding Claims additionally comprising a flavoring agent selected from the group consisting of : menthol, peppermint, spearmint, raspberry, cherry, orange, vanilla, anise, blueberry, banana, chocolate, caramel, strawberry, lemon, grape and mixtures thereof.

8. A pharmaceutical composition according to any one of the preceding Claims additionally comprising a releasing agent selected from the group consisting of: polysorbate 80, sodium lauryl sulfate, magnesium stearate and mixtures thereof.

9. A pharmaceutical composition according to any one of the preceding Claims additionally comprising a cooling agent selected from the group consisting of: 3-1-methoxypropane 1,2-diol, N-ethyl-p-methane-3-carboxamide and mixtures thereof.

10. A pharmaceutical composition according to any one of the preceding Claims wherein the ratio of said magnesium aluminum silicate to said phenylpropanolamine and said chlorpheniramine is 1 to 5.0 and 1 to 0.8 respectively.

IPC 6 A61K9/14 A61K9/00 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,92 17164 (THE PROCTER & GAMBLE COMPANY) 15 October 1992 see claims 1-12 see page 3, line 6 - line 35 see page 5, line 1 - line 24	1-9
X	EP,A,0 239 542 (WARNER-LAMBERT COMPANY) 30 September 1987 cited in the application see claim 1 see page 4, line 9 - line 26 see page 4, line 63 - page 5, line 12 see page 5, line 42 - page 6, line 12 see example 4	1-5,7
P,X	WO,A,94 20074 (THE PROCTER & GAMBLE COMPANY) 15 September 1994 see the whole document	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
27 January 1995	17.02.95
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Ventura Amat, A

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